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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P92698WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01644	28/04/2000	01/05/1999
International Patent Classification (IPC) or national classification and IPC A01N47/44		
Applicant BIOINTERACTIONS LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/11/2000	08.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Donovan-Beermann, T Telephone No. +49 89 2399 8213

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01644

I. Basis of the report,

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-30	as originally filed				

Claims, No.:

1-27	as received on	28/05/2001	with letter of	28/05/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Ad Section V:

The present application relates to polymeric materials and methods for their preparation, wherein a biguanide compound having antimicrobial properties is pendantly bound to the polymer via some but not all of the secondary amine nitrogen atoms of the biguanide group -NH-C(NH)-NH-C(NH)-NH- via a substituted urea linkage, a substituted thiourea linkage, an N,N-disubstituted hemiaminal or aminal linkage, or a tertiary amine linkage. The biguanide is preferably polyhexanide or chlorhexidine. The resulting antimicrobial materials are useful in various medical applications and eg. for contact lenses.

The amendments to the claims and description are considered allowable according to Art.34(2)(b) PCT in that they do not extend the scope of the application beyond that of the disclosure as originally filed.

EP-A-460385 (D1, = US-A-5142010, cited in the application) discloses antimicrobially active polymers having pendant biguanide groups (see page 2, line 50-page 4, line 28). The polymers may be used as bulk polymers, or as coatings, in fabrics etc., and applied in various methods to various applications such as medical-surgical, food preservation etc. (see page 2, lines 1-8). In order to prepare the polymers, a monomer is prepared which contains a polymerisable group attached through a secondary nitrogen to the biguanide group.

GB-A-2085454 (D2) discloses antimicrobial polymers for use as biomedical materials such as in the manufacture of contact lenses (see page 1, lines 5-18). Monomers are prepared which comprise an antimicrobial *substituent*, and a small quantity of these monomers are used in the polymer formation (see page 1, lines 19-29 and 45-55). The antimicrobial agent which is incorporated into the polymer is eg. chlorhexidine diacetate (see page 1, lines 36-42).

EP-A-103776 (D3) discloses the coupling of pesticidally active agents having an Zerewitinoff-active hydrogen with polyetherisocyanates, which produces a polymer with pendant active groups (see page 3, line 1-page 4, line 9). The pesticidally active agent is eg. a guanidine (see page 4, lines 18-19 and page 5, lines 1-4). Biguanides are

however not mentioned.

JP-A-62230806 (D4) discloses polymers and methods for their preparation which contain pendant guanidine groups. However, biguanides are not included.

None of the above prior art documents disclose the present types of linkage used, ie. the substituted urea linkage, substituted thiourea linkage, N,N-disubstituted hemiaminal or aminal linkage, or tertiary amine linkage. Thus the subject matter of the present claims is novel with respect to the abovementioned prior art (Art.33(2) PCT).

The materials and methods thus provide further useful materials not suggested by the prior art. On the basis of this, inventive step can be acknowledged (Art.33(3) PCT).

Ad Section VI:

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
US-A-5298916	27.07.99	22.01.98	-

Ad Section VII:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

CLAIMS

1 A polymeric material incorporating an infection resistant biguanide compound pendant to the polymer chain, being chemically bound thereto through some but not all of the amine nitrogen atoms of the infection resistant biguanide compound.

2 A polymeric material according to claim 1 wherein the pendant infection resistant biguanide compound is chemically bound to the polymer chain through secondary amine nitrogen atoms of the -NC-C(NH)-NH-C(NH)-NH- biguanide group or groups of the biguanide compound.

3 A polymeric material according to claim 1 or claim 2 wherein the biguanide compound is the residue of chlorhexidine or polyhexanide.

4 A polymeric material according to claim 2 or claim 3 wherein the said chemical binding to secondary amine nitrogen atoms is by means of a substituted urea linkage, or a substituted thiourea linkage, or a N,N-disubstituted amide linkage, or a N,N-disubstituted hemiaminal or aminal linkage, or a tertiary amine linkage.

5 A medical device comprising a polymeric material incorporating a pendant infection resistant biguanide compound chemically bound to the polymer through some but not all of the amine nitrogen atoms of the infection resistant biguanide compound.

6 A medical device according to claim 5 wherein the pendant infection resistant biguanide compound is chemically bound to the polymer chain through secondary amine nitrogen atoms of the -NC-C(NH)-NH-C(NH)-NH- biguanide group or groups of the biguanide compound.

7 A medical device according to claim 5 or claim 6 wherein the medical device is formed from or coated with the polymeric material incorporating the infection resistant biguanide compound, or the medical device is first formed from or coated with polymeric material which is thereafter chemically bound to some but not all of the nitrogen atoms of the infection resistant biguanide compound, or the medical device is first formed from or coated with polymeric material which is thereafter chemically bound to the residuum of a non-polymeric compound that has been bound to some but not all of the nitrogen atoms of the infection resistant biguanide compound.

8 A medical device according to any one of claims 5 to 7 wherein the biguanide compound is a residue of chlorhexidine or polyhexanide.

9 A medical device according to any one of claims 6 to 8 wherein the said chemical binding to secondary amine nitrogen atoms is by means of a substituted urea linkage, or a substituted thiourea linkage, or a N,N-disubstituted amide linkage, or a N,N-disubstituted hemiaminal or aminal linkage,or a tertiary amine linkage.

10 A medical device according to any one of claims 5 to 9 formed as a contact lens or intra-ocular lens.

11 A method of making an infection resistant polymeric material which comprises chemically binding reactive sites on a polymeric material with some but not all of the amine nitrogen atoms of an infection resistant biguanide compound.

12 A method according to claim 11 wherein the amine nitrogen atoms that are bound to the reactive sites include secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of the biguanide compound..

13 A method according to claim 11 or 12 which comprises the preliminary step of forming a partial free base of the biguanide compound before binding the reactive sites with the nitrogen atoms.

14 A method according to any one of claims 11 to 13 wherein the reactive sites comprise isocyanate, isothiocyanate, epoxide, acid chloride, acid anhydride, aldehyde, ketone or unsaturated sites.

15 A method according to any one of claims 11 to 13 wherein the reactive sites comprise hydroxyl, carboxyl or amino groups and the binding to the nitrogen atoms is carried out in the presence of a carbonyl diimidazole or carbidomide coupling agent.

16 A method of making an infection resistant polymeric material which comprises modifying a polymer precursor by chemically binding some but not all of the amine nitrogen atoms of an infection resistant biguanide compound with reactive sites on the polymer precursor, and thereafter converting the so modified polymer precursor to an infection resistant polymeric material by a method including a polymerisation step.

17 A method according to claim 16 wherein the amine nitrogen atoms bound to the reactive sites include secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of the biguanide compound.

18 A method according to claim 16 or 17 which comprises the preliminary step of forming a partial free base of the biguanide compound before binding the reactive sites with the nitrogen atoms.

19 A method according to any one of claims 16 to 18 wherein the reactive sites comprise isocyanate, isothiocyanate, epoxide, acid chloride, acid anhydride, aldehyde, ketone or unsaturated sites.

20 A method according to any one of claims 16 to 18 wherein the reactive sites comprise hydroxyl, carboxyl or amino groups and the binding to the nitrogen atoms is carried out in the presence of a carbonyl diimidazole or carbidomide coupling agent.

21 A method according to any one of claims 16 to 20 wherein the polymer precursor also contains acrylate, methacrylate, allyl or vinyl groups, and the polymerisation step is carried out by polymerising the modified polymer precursor through the said groups.

22 A method of making an infection resistant polymeric material which comprises modifying a non-polymeric compound by chemically binding some but not all of the amine nitrogen atoms of an infection resistant biguanide compound with reactive sites on the non-polymeric compound, and thereafter chemically binding the so modified compound to a polymeric material.

23 A method according to claim 22 wherein the amine nitrogen atoms bound to the reactive sites include secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of the biguanide compound.

24 A method according to claim 22 or 23 which comprises the preliminary step of forming a partial free base of the biguanide compound before binding the reactive sites with the nitrogen atoms.

25 25 A method according to any one of claims 22 to 24 wherein the reactive sites comprise isocyanate, isothiocyanate, epoxide, acid chloride, acid anhydride, aldehyde, ketone or unsaturated sites.

26 A method according to any one of claims 22 to 24 wherein the reactive sites comprise hydroxyl, carboxyl or amino groups and the binding to the nitrogen atoms

is carried out in the presence of a carbonyl diimidazole or carbidomide coupling agent.

27 A method according to any one of claims 22 to 26 wherein the non-polymeric compound also contains acrylate, methacrylate, allyl or vinyl groups, and the modified compound is chemically bound to a polymeric material through the said groups.

28 A method according to any one of claims 11 to 27 wherein the resulting polymer containing biguanide groups is subsequently blended with other polymeric material to form an infection resistant polymer blend for use in forming an article of manufacture.

29 A method according to claim 28 wherein the resulting polymer containing biguanide groups is subsequently blended with medically acceptable polymeric material to form an infection resistant medical polymer blend for use in the manufacture of a medical device.

30 A method according to claim 29 wherein the resulting polymer containing biguanide groups is subsequently blended with ocularly acceptable lens material to form an infection resistant ocular polymer blend for use in the manufacture of a contact or intra-ocular lens.

31 A method according to claim 30 wherein the resulting polymer containing biguanide groups includes acrylate, methacrylate, allyl or vinyl groups, and the polymer is subsequently copolymerised with ocularly acceptable lens material to form an infection resistant ocular polymer for use in the manufacture of a contact or intra-ocular lens.